Randomization/Selection of Endpoints
Lecture 2
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OUTLINE

Randomization

- Key methodologic design feature
- Intention to treat principle
- How to do the scheme
- How to administer

Endpoint Selection

- Key clinical design feature
- Considerations for good endpoints
- Surrogate endpoints

Why Randomize?

- **Best way to assure compatibility**

- **In the long run balance of factors**
  Known
  Unknown

- **Statistical hypothesis test based on random assignment**

- **Selection is impartial: "dice not trying to prove a point"**

- **Must convince others of validity of comparison**

Randomization

FIXED ALLOCATION: Assigns with pre-specified probability (not necessarily, though usually, equal)

ADAPTIVE: Changes probabilities during study

Baseline adaptive:
- on basis of number per group
- on basis of variables

Responsive adaptive: - depends on prior outcome

Assumes
- rapid response
- stable population source

Internal Validity

compare treatments

External Validity/ Generalizability

extrapolate to other patients

Not realistic to find a random sample of patients for recruitment (at the very least they have to consent)

More important to establish efficacy of treatment before deciding if it can be broadly applied

A Classification of Trials

Explanatory – acquire information on the true treatment effects

Pragmatic – make a decision about therapeutic strategy after taking into account "cost" (withdrawals, side effects) of administering treatment

- **most closely resembles clinical scenario**
- **treatment policy**
- **treatment intention**

Intention to Treat Principle

Intention to treat analysis based on random assignment

"Once randomized – always analyzed"

- **entrance criteria**
- **treatment actually received**
  - **"Crossovers"**
- **withdrawal from treatment**
- **deviation from protocol (adherence to protocol)**

Adherence to Intervention

Coronary Drug Project

Lipid lowering drugs after myocardial infarction

	Mortality
clofibrate	18.2%
placebo	19.4%

	Overall	Clofibrate Adherence	
		≥ 80	< 80%
Clofibrate	18.2%	15.0%	24.6%

Percent Mortality in the Coronary Drug Project

		Drug Adherence	
	Overall	$\geq$ 80%	$<$ 80%
Clofibrate	18.2%	15.0%	24.6%
Placebo	19.4%	15.1%	28.2%

Should We Only Do One Analysis?

Intention-to-treat primary espoused by FDA and NIH

Secondary analysis

Efficacy subset analysis

Are the results similar?Try to reconcile

Compare baseline characteristics of adheres versus non-adherers

Can show not comparable but can't prove they are comparable

Make various assumptions for missing outcome data

- Last observation carried forward
- Worst case scenario

Practical Issues

Minimize lost to follow-up

Even if poor or no adherence follow-up patients

"Fire the statistician if doing so frees enough resources to allow completed data to be obtained. Complete data worth innumerable statistical models to adjust for ignorance"

Patrick Shrout

How To Do The Scheme

Simple randomization

Biased coin, urn models

Example:

Start with 2 balls, one black and one white

Draw–replace and add one of opposite color

Prevents imbalance with high probability early on

Random permuted block

Balance at the end of block

Could predict with unmasked trial

Blocks Of Size 4

$$\binom{4}{2} = \frac{4!}{2!2!} = \frac{4*3*2*1}{2*1*2*1} = 6$$

1) 1100
2) 1010
3) 1001
4) 0110
5) 0101
6) 0011

How To Use Blocks When Treatment Is Not Masked

Choose the block sizes at random, too

Example: 2 treatments, equal allocation

Block sizes 4, 6, and 8 – random order

Balance in each block

Should You Stratify?

Factors:

- Clinical sites – generally yes
- Prognostic variables – generally not necessary

Issues:

Size

Practical considerations

Often governed by custom rather than statistical justification

Stratified ANALYSIS is usually preferred

Minimization

Advantages:

- **Balance several prognostic factors**
- **Balance marginal treatment totals**
- **Good for small trials (<100 patients)**
- **Computer makes this fairly easily**

Disadvantages:

- **Can't prepare treatment assignment Scheme in advance**
- **Need up-to-date record**
- **Not really random – could predict but can introduce random element by using say 3/4, 1/4**

Table 5.7. – Treatment Assignments by the Four patient Factors for 80 Patients in an advanced Breast Cancer Trial

Factor	Level	No. on each treatment A	B	Next patient
Performance status	Ambulatory	30	31	←
	Non-ambulatory	10	9	
Age	<50	18	17	←
	≥50	22	23	
Disease-free interval	<2 years	31	32	
	≥2 years	9	8	←
Dominant metastatic lesion	Visceral	19	21	←
	Osseous	8	7	
	Soft tissue	13	12	

Thus, for A this sum = 30 + 18 + 9 + 19 = 76
while for B this sum = 31 + 17 + 8 + 21 = 77

Pocock S. Clinical Trials: *A Practical Approach.* John Wiley & Sons, Chichester, England, 1991, p. 85.

Steps in the Randomization of a Patient

Check eligibility

Informed consent

Formal identification

RANDOMIZE

Confirmation of patient entry

How Random Treatment Assignments Are Made

Model: Slips in a hat or flipping a coin

Masked drugs numbered and given in order: pharmacy, drug manufacturer

Envelopes

Telephone to central unit

- **Real person**
  - **trained**
  - **untrained**
- **Computer**
- **Automated answering machine**
- **Microcomputer at the site**
  - **local**
  - **central computer**

Clinical Hypothesis

Patient selection

Intervention (treatment)

Endpoint (timing)

Endpoints–outcome–response variable

- Typical endpoints
  - mortality
  - death from specific cause
  - incidence of a disease
  - symptomatic relief

- Key principle: pick one primary endpoint
  - can then specify numerous secondary endpoints

- Type of data
  - yes or no, dead or alive, success or failure (dichotomous)
  - continuous
  - time to event (censoring)
  - frequency of events
  - ordinal scale

Is change from baseline a good endpoint?

Not as often as one might think.

- Unless pre and post are highly correlated (>.5) sample size is greater than using post value.
- Often not good data on standard deviation of change.
- Randomization produces groups similar at baseline
- Can adjust for baseline level as covariate

Masked Evaluation of Endpoint

- Most behavioral interventions can't be masked: patients or those delivering intervention.

- Can evaluator be masked? Strong design feature.

  Examples: Measure of blood pressure, pain scale.

Endpoint Issues

Good endpoints

- Primary response must be capable of being assessed in everyone – minimize missing data
- Measured in the same way (standard blood pressure measuring)
- Uniform assessment – train evaluators
- Reliability

Composite Endpoints

ex: death or nonfatal MI
hospitalization or emergency room visit

One event per subject

Behavioral program to reduce obesity Possible endpoints:

- weight at 3 months
- weight at 5 years
- body fat at fixed time point
- onset of diabetes
- reduction in need for diabetic meds
- blood pressure
- lipid measures
- MI/death
- death

Behavioral Intervention for Problem Alcohol Drinkers

Possible Endpoints:

Average drinks per week

Health utilization, hospital days and emergency room visits

Surrogate Endpoints

Motivation: need for rapid reliable evaluation of promising new interventions

Substitute for a clinically meaningful endpoint (feel good, function better, live longer)

A laboratory measurement or physical sign

Cheaper, faster, easier

Requirement: correlate with true clinical outcome (This is a big assumption.)

Surrogate Endpoints – Examples

Smoking cessation – lung cancer, cardiovascular disease

Bone density – osteoporosis

Proliferation of breast tissue – breast cancer

Blood pressure – stroke, myocardial infarction

Surrogate Arrhythmia Example

- Coronary arrhythmias are associated with sudden death
- Drugs developed to suppress arrhythmias
- Approved for special use
- Increased off label use
- Little data on mortality effect

Cardiac Arrhythmia Suppression Trial (CAST-1)

- Two drugs (Encainide, Flecainide)
- Randomized, double masked, placebo control
- Testing if suppression of arrhythmias in MI patients reduces
  - sudden death
  - total mortality
- Expected a 30% reduction in mortality
- 1455 patients randomized
- 3 years average follow-up

CAST–1
Early Interim Results

	Drug	Placebo	P
N	730	725	
Sudden death	33	9	.0006
Total death	56	22	.0003